mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Original article

Airborne fungus exposure prior to hospitalisation as risk factor for mould infections in immunocompromised patients

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Summary

The aim of this study was to investigate the relationship between fungal exposure prior to hospitalisation and ensuing onset of invasive mould infections (IMI) in patients at risk. Patients admitted to the Department of Haematology, Oncology and Transplant Surgery of the Medical University Innsbruck received a questionnaire regarding fungal exposure prior to hospital stay. Questions inquired heavy fungal exposures up to 5 days before hospitalisation. A total of 234 patients were enrolled in this study. Multiple fungus exposures were associated with the onset of community-acquired IMI in patients with haematological malignancies. In univariate analysis, haematological malignancies ($P = 0.013$) and allergy to dust, pollen or moulds ($P = 0.015$) were significantly associated with fungal infections. In multivariate analysis, logistic regression showed that haematological patients ($P = 0.015$) and patients with allergy ($P = 0.015$) were significantly more frequently infected with fungi. Hospital-independent fungal sources highlight risk-factors for IMI in severe immunocompromised patients and the rate of community-acquired IMI does increase.

Key words: Airborne fungus exposure, environmental risk factors, invasive mould infections, aspergillosis.

Introduction

The most well-known opportunistic mycoses are caused by *Candida* and *Aspergillus* species.[1] *Aspergillus* spp. are common throughout the world and ubiquitous in air, soil and decaying matter.[2] Invasive mould infections (IMI) are a significant determinant of the morbidity and mortality of patients undergoing immunosuppressive therapy.[3–5] *Aspergillus fumigatus* is most frequently isolated from invasive aspergillosis (IA) followed by *A. flavus*, *A. niger* and *A. terreus*.[6] The main entry route of *Aspergillus* and other moulds is inhalation of conidia.

In susceptible patients, fungal air concentrations and the duration of exposure within the hospital display important risk factors in the onset of nosocomial-acquired infections.[7–10] The role of hospital-independent fungal spread sources, e.g. in the private homes are not known. However, environmental conditions, home characteristics and personal behaviour might play a crucial role in acquiring IA or IMI. Previous work has highlighted that about 50% of humans show lung colonisation with airborne fungi.[11]

This study evaluated prehospital fungus exposures of patients admitted to the Department of Haematology and Oncology and to the Department of Visceral, Transplant and Thoracic Surgery, Centre of Operative Medicine, Innsbruck Medical University. We investigated the relationship between fungal exposure prior to

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Submitted for publication 17 January 2011
Revised 21 June 2011
Accepted for publication 26 June 2011

doi:10.1111/j.1439-0507.2011.02073.x

hospitalisation and the ensuing onset of IMI in patients at risk. Our goal was to identify whether such sources highlight riskfactors for IMI.

Materials and methods

Study cohort

Patients admitted to the Department of Haematology and Oncology or to the Department of Transplant Surgery of the Innsbruck Medical University received a structured questionnaire regarding their fungal exposure prior to hospitalisation. Patients were treated for haematological malignancies or underwent solid organ transplantation. The hospitalised patients were nursed in settings equipped with high efficient particulate air filter systems (HEPA). Physicians were not informed of heavy fungal exposure nor of any other risk factors, which were collected via data collection. The study protocol was approved by the local Ethics Committee.

Environmental samples in the protected HEPA-units

Environmental samples were collected routinely by the hospital hygiene team and twice a month to exclude fungus spread in the clinical settings. Air samples were taken during the course of normal hospital activity with a Surface Air System Sampler (SASS) (Admeco-Impactor, Type FH2, Switzerland); 150 and 100 l were collected and the SASS was loaded with autoclaved Sabouraud dextrose agar (SAB) plates.

Questionnaire

Questions inquired about heavy fungal exposures (e.g. visible fungal contamination indoors) up to 5 days prior to hospitalisation. Human behaviour (smoking vs. non-smoking, housing and living conditions), demographic variables including profession, private and business environmental factors were analysed in detail. Working and living sites (country or urban), building structures (new or old buildings; < or >50 years), frequencies of cleaning, exposures to dampness, potted plants, pets, biowaste, construction and reconstruction work, and inside moulds infestation were investigated. In addition, surveys whether patients suffered from allergy to pollen, moulds and dust were performed. The question-answer-reply consisted of either yes or no plus a scoring of low, medium and heavy. Finally, the minimum and maximum exposed time-span was asked to be declared. In case of patients who needed help to ascertain whether indoor fungal decay was evident, their homes/business suites were analysed by us.

Patients and invasive fungal infections

The European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) consensus criteria were used to define IMI.[12] Diagnostic approaches and therapeutic interventions were performed following standard rules and protocols.[13] Fungal surveillance cultures from throat and nose were routinely performed once a week in patients with haematological malignancies. A community-acquired case was defined as one in which clinical evidence of infection was present on admission, appeared within the second week of admission, or more than 2 weeks after discharge.[14] A nosocomial case was defined as an infection occurring during hospitalisation that was not present or incubating on admission, or a case occurring within 2 weeks of discharge.[14]

Statistical analyses

Absolute and relative frequencies were calculated for different measures in relation to diseases and infection. Chi-square test was used for statistical comparison between subgroups. Differences according to age were assessed by t-test for independent samples. Fungal exposures were compared between the groups using contingency table analysis and Fisher's exact test. Logistic regression analysis was calculated to multivariately assess predictors for fungal infections. $P < 0.05$ was considered statistically significant.

Results

In total, 234 patients were enrolled in this questionnaire-based study. Overall, 19% of patients were smokers, 22% suffered from a type I hypersensitivity to pollen, dust or moulds, 62% live in old buildings, 73% were people living in country locations, 82% and 92% were exposed to any outdoor or indoor fungus sources; 83% and 87% of haematological and transplant patients belong to the country population. Overall, 8% developed IA or IMI (proven and probable). By analysing all patients' data together, no significant differences, except gender, were observed in age, human behaviour, living conditions and fungus exposure inside and outside (Tables 1 and 2). Fourteen patients with haematological malignancies and four with solid organ transplants developed IMI ($P = 0.01$), 88% were community-acquired cases. Detailed charac-

Table 1 Characteristics of the subjects enrolled in the questionnaire based trial.

	Haematological malignancies, *n* (%)	Solid organ transplant recipients, *n* (%)	*P**
No. of patients	116 (100)	118 (100)	
Age, mean years ± SD	48.57 ± 5.9	50.23 ± 6.8	0.36 (*t* test)
Female	56 (48)	32 (27)	
Male	60 (52)	86 (72)	0.001
Underlying diseases			
AML	44 (37)		
NH	25 (21)		
ALL	10 (8)		
MM	10 (8)		
STU	6 (5)		
CLL	2 (2)		
MS	2 (2)		
CML	2 (2)		
AA	2 (2)		
Others	15 (13)		
Organ transplantation			
Kidney		53 (46)	
Lung		34 (30)	
Pancreas		26 (22)	
Others		3 (2)	
Non-smokers	90 (78)	100 (85)	
Smokers	26 (22)	18 (15)	0.16
No allergy	92 (80)	91 (77)	
Allergy	24 (20)	27 (23)	0.68
Urban citizens	29 (26)	35 (29)	
Country citizens	87 (74)	83 (71)	0.42
Live in new houses	71 (61)	74 (63)	
Live in old houses	39 (39)	44 (37)	0.77

AML, acute myelogeneous leukaemia; NHL, non-hodgkin lymphoma; ALL, acute lymphoblastic leukaemia; MM, multiple myeloma; STU, solid tumours; CLL, chronic lymphatic leukaemia; MS, myelodysplastic syndrome; CML, chronic myelogenous leukaemia; AA, aplastic anaemia

*Determined by χ^2 test, unless otherwise indicated.

teristics are given in Table 3. In univariate analysis, haematological malignancies ($P = 0.013$) and allergy ($P = 0.015$) were significantly associated with fungal infections (Table 4). In multivariate analysis, logistic regression showed that haematological patients ($P = 0.015$) and patients with allergy ($P = 0.015$) were significantly more frequently infected with fungi. Uni- and multivariate analyses were similar; however, the association between allergy and fungal infection was only significant in haematological patients. There were 7/24 infections in allergy patients and 7/92 infections in patients without allergy ($P = 0.004$). Exposures to environmental triggers for acute myelogeneous leukaemia (AML) patients are summarised in Fig. 1.

The time-span for indoor and outdoor fungus exposure was 5.6 days (range, 45 min–24 days) and 3.5 h (range, 5 min–7 h).

Fungal colonisation was identified in only one patient and the inside-air hospital survey generated very low fungal densities with a mean of 0.017 colony forming units (cfu) m^{-3}. These low counts exclude transmissions in the protected settings.

Homes and/or business suites of four patients were visited and heavy indoor mould infestation was identified. In these cases either >1000 cfu m^{-3} in the air (volume and time of sampling) or extensive fungal growth on the walls were identified. *Cladosporium* spp., *Alternaria* spp., *A. fumigatus, A. flavus* and others were observed.

Discussion

This study showed that hospital-independent fungal exposure was associated with the onset of IA and IMI in patients with haematological malignancies (e.g. AML) and solid organ transplantations (e.g. lung transplant recipients) receiving extensive immunosuppressive agents to treat allograft rejection. Community-acquired IMIs were frequently observed and the private and professional fungus load display risk factors in the onset of IMI only in severely immunocompromised patients.

Traditionally patients at highest risk for infection and invasive disease were those with either profound or prolonged neutropenia[15]; IA was frequently of noscomial-origin.[16] In the hospital setting, therefore the use of hepafiltration and in particular, laminar flow is highly recommended to eliminate fungal spores from the environment.[6,17] This resulted at least in a slightly reduction of IA but did not reduce it to zero.[6] Probably because patients were already colonised by *Aspergillus* at time of admission to the hospital.[11] However, the temporal association of invasive fungal infections had thus shifted to a bimodal distribution with the highest risk seen early after transplantation and a second peak in incidence occurring more than 100 days post-transplantation.[5,18–20] This was possibly caused by changes in transplant procedures and resulted in a reduction in duration of neutropenia and in an increase of incidence and severity of graft-vs.-host disease.[4,19–21] These changing practices led patients at continuing risk to be discharged home and into an unprotected environment.

To gain insights into the risks of infection, a large cohort of patients with haematological malignancies and solid organ transplantations were examined. Heavy exposure to typical fungus sources occurred frequently,

Table 2 Subject-reported exposure to potential private and business environmental fungus sources.

	Haematological malignancies, *n* (%)	Solid organ transplant recipients, *n* (%)	*P**
General fungal exposure inside	109 (92)	107 (98)	0.97
Detailed exposure inside			
0 No exposure	9 (8)	9 (8)	0.97
1 > 5 potted plants	32 (27)	33 (28)	0.86
2 Biowaste container	34 (29)	41 (35)	0.28
3 Mould manifestation	26 (22)	18 (15)	0.20
4 Dusty household[1]	13 (11)	10 (9)	0.53
5 Pets (birds) in household[2]	4 (3)	5 (3)	0.71
Multiple exposure inside	91 (77)	83 (71)	0.32
General fungal exposure outside	102 (86)	92 (79)	0.06
Detailed exposure outside			
0 No exposure	16 (14)	24 (21)	0.14
1 Construction	47 (40)	41 (35)	0.47
2 Biowaste container	29 (25)	32 (28)	0.59
3 Agriculture/Farmer	15 (13)	13 (11)	0.72
4 Bird droppings (excreta)	6 (5)	4 (3)	0.53
5 Reconstruction	5 (3)	2 (2)	0.25
Multiple exposure outside	66 (56)	59 (51)	0.43

*Determined by χ^2 test, unless otherwise indicated.

[1]Cleaning frequency (vacuum cleaner) is less than once in 2 weeks, dust occurs extensively.

[2]This includes also rodents, doves and dove droppings.

Table 3 Characteristics of invasive fungal infections during the study period.

Category, characteristics	Haematological malignancies	Solid organ transplant recipients	*P**
Time span hospitalisation (days)	8, range 6–43	6, range 7–23	0.54 (Mann–Whitney test)
Pathohistology (only)	4	0	
EORTC[1]	14	4	0.01
Proven	10[2]	2[3]	
Probable	4	2	
Possible	0	0	
Nosocomial IMI[4]	2	0	
Community-acquired IMI[5]	12	4	0.04
History of IMI	0	2	
Fungal carrier	1	0	

*Determined by χ^2 test, unless otherwise indicated.

[1]European Organization for Research and Treatment of Cancer.

[2]80% of patients suffered of acute myelogeneous leukaemia.

[3]Patients had graft failure and were therefore under severe immunosuppression and corticosteroids.

[4]Invasive mould infections.

[5]All patients suffering from community-acquired IMI (16) had multiple fungal exposure inside and outside.

either at home or in the business setting. About 70% of our study population had multiple indoor fungal exposures and 81% had multiple exposures during business and leisure practices. The time-period exposed to fungus sources was rather long with 5.6 and 3.5 days for indoor and outdoor, respectively. Construction (38%), biowaste (32%), potted plants (30%) and indoor fungus decay (16%) were the important fungus sources. We assume that these conditions support an increase of community-acquired infections. In our patient-population, 88% of IMI was acquired during home-stay.

Table 4 Relative risk factors for invasive fungal infections.

	No infection (*n* 216)		Infection (*n* 18)		
Risk factor	Count	*n* %	Count	*n* %	*P**
Solid organ transplant recipients	114	52.8	4	22.2	
Haematological malignancies	102	47.2	14	77.8	0.013
Female	82	38.0	9	33.3	
Male	134	62.0	12	66.7	0.697
Non-smoker	177	81.9	13	72.2	
Smoker	39	18.1	5	27.8	0.310
No allergy	173	80.1	10	55.6	
Allergy	43	19.9	8	44.4	0.015
Country citizens	157	72.7	13	72.2	
Urban citizens	59	27.3	5	27.8	0.966
Live in new houses	142	65.7	11	61.1	
Live in old houses	74	34.3	7	38.9	0.692

*Determined by χ^2 test, unless otherwise indicated.

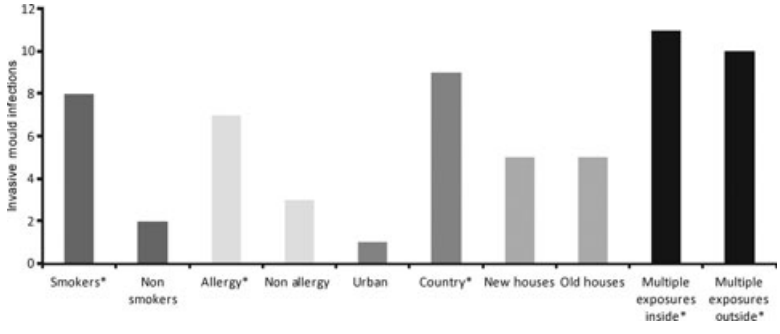

Figure 1 Environmental exposures and the onset of invasive mould infections in acute myelogeneous leukaemia (AML) patients. *A subgroup analysis showed AML patients being more at risk for invasive mould infections with the underlying conditions.

So far, it is not clear from our study what the incubation period between exposure and the development of diseases is. For one heart transplant recipient, it was documented that there was a 3-month time lag between the identification of *Aspergillus* in bronchoalveolar lavage fluid and subsequent development of disease.[22]

Since *Aspergillus* is so common in the environment, most people breathe in *Aspergillus* spores every day. For individuals with healthy immune systems, this does not cause any harm as the immune system is able to get rid of the spores. The development of IA or IMI requires both: exposure to relevant inoculum and a susceptible host. It is not known what the infectious inoculum for IMI is, but this factor may depend upon the host. Overall, 16% of patients had indoor mould decay in their adjacencies and in four cases, in which the patients were not sure about the fungal infestation, we proofed this evidence. The latter suffered from chronic myelogenous leukaemia (CLL) (n = 1), multiple myeloma (MM) (n = 1) or had received an organ transplantation (n = 2). Three of them did never develop IMI or IA with the exception of one. This patient did well during the early post-transplant period but suffered latter (8 months) from graft failure II and post-transplant lymphoproliferative diseases. During this severe immunosuppression (ciclosporin, cortisone and alemtuzumab), the patient developed community-acquired IMI. The patient had two risk parameters at the same time: heavy fungus exposure and lack of an adequate immune response. A fungal surveillance study in asthma children appeared also the private fungus load to have a significant impact on diseases.[23]

Many studies have attempted to evaluate the importance of fungal aerobiology during hospitalisation.[8–10,15,24,25] Most authors recommend *Aspergillus* air counts of less than 5 cfu m^{-3} in protective isolation suites.[17,26–28] Yet, Rhame *et al.* reported of risk at 0.9 cfu m^{-3}.[28] However, a strict correlation between the *Aspergillus* cfu m^{-3} and the incidence of IMI has not been documented.[26] So far, thisstudy shows that patients suffering from AML and organ transplant recipients with graft failure and extensive immunosuppressive treatment are at highest risk when exposed to two or more hospital-independent fungal sources. Furthermore, haematological patients seem to be at

highest risk when suffering from allergy to dust, pollen and/or moulds ($P = 0.015$). The association of a type I allergy to airborne allergens and the onset of IA or IMI need to be further investigated. The reason for this phenomenon is not known. One explanation could be that an extensive dust exposition leads to an extensive allergen (mould) exposition, which in turn allows for hypersensitivity and fungal uptake via inhalation. Living in rural areas is associated with agriculture, farming, animals, hay, straw, grassland and dung; these are typical fungus sources.[29,30] Half of our patient population at the University Hospital of Innsbruck are people living in country locations, a fact that could generally contribute to a higher incidence of IA. However, we have to account that these details derive from the patients query and it is presently not known, whether all cases are proved by a specialist. We were able to identify adequate records in 56% of patients with AML.

Our study has some limitations: we did not investigate the fungus carrier status on admission via panfungal PCR or via the galactomannan assay, so we do not know whether the fungus at home/business suite is the one responsible for infection. By reason of the lack of high sensitivity and specificity and the presence of false positive blood samples in a PCR surveillance study we have not done such examinations.[31,32] The high biodiversity of *Aspergillus* spp. contributes to a lack of genotype correlation in environmental and infecting agents.[33,34] Moreover, during the study period, we had a low number of cases with proven IMI in the transplant setting. Anyway, the previous study goal was to investigate whether a heavy fungus exposure is correlated with the onset of IA or IMI.

The best way to prevent and control community-acquired fungal-diseases such as IA or IMI is to prevent exposure to fungi in patients at risk. Immunosuppressed persons should avoid dusty environments, mould decay, biowaste and activities where dust or fungus exposure exist. Wearing adequate masks in the private setting should help in some circumstances. However, it is probably impossible to completely avoid breathing in some *Aspergillus* spores. Medical doctors and healthcare practitioners should focus their patients' education on this strategy. The first step in preventing IMI or IA should be an individualised intervention programme including identification of high-risk patients and high-risk environments. The role of prophylaxis in this setting needs to be addressed in more detail.

In conclusion, our data uncover the role of private and business fungus load in the onset of IMI or IA. AML and solid organ transplant patients under severe immunosuppression are at highest risk to develop community-acquired IMI when exposed to two or more fungus sources. Haematological patients are more vulnerable to contract fungal infections when they suffer from allergies (dust, pollen or moulds).

Conflicts of interest

None declared.

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